



SITraN

Sheffield Institute for Translational
Neuroscience



New Developments in the Symptomatic Management of ALS/MND

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TC-29 TEACHING COURSE

***Motor Neuron Disease: An update on diagnosis, management and
pathophysiology.***

XXII World Congress of Neurology Santiago Chile 2015

Pamela Shaw - Disclosures

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Biogen

Orion

Re neuron

Learning Objectives

- 1. To understand the value of good symptomatic care for quality of life and life expectancy in ALS/MND.
- 2. To gain awareness of recent research providing an evidence base for best practice symptomatic management.
- 3. To learn about new developments in the management of respiratory and nutritional complications of ALS/MND
- 4. To learn how bioengineering research can produce new devices to support specific aspects of neuromuscular weakness.
- 5. To gain awareness of prospects for the development of new neuroprotective therapies for ALS/MND.

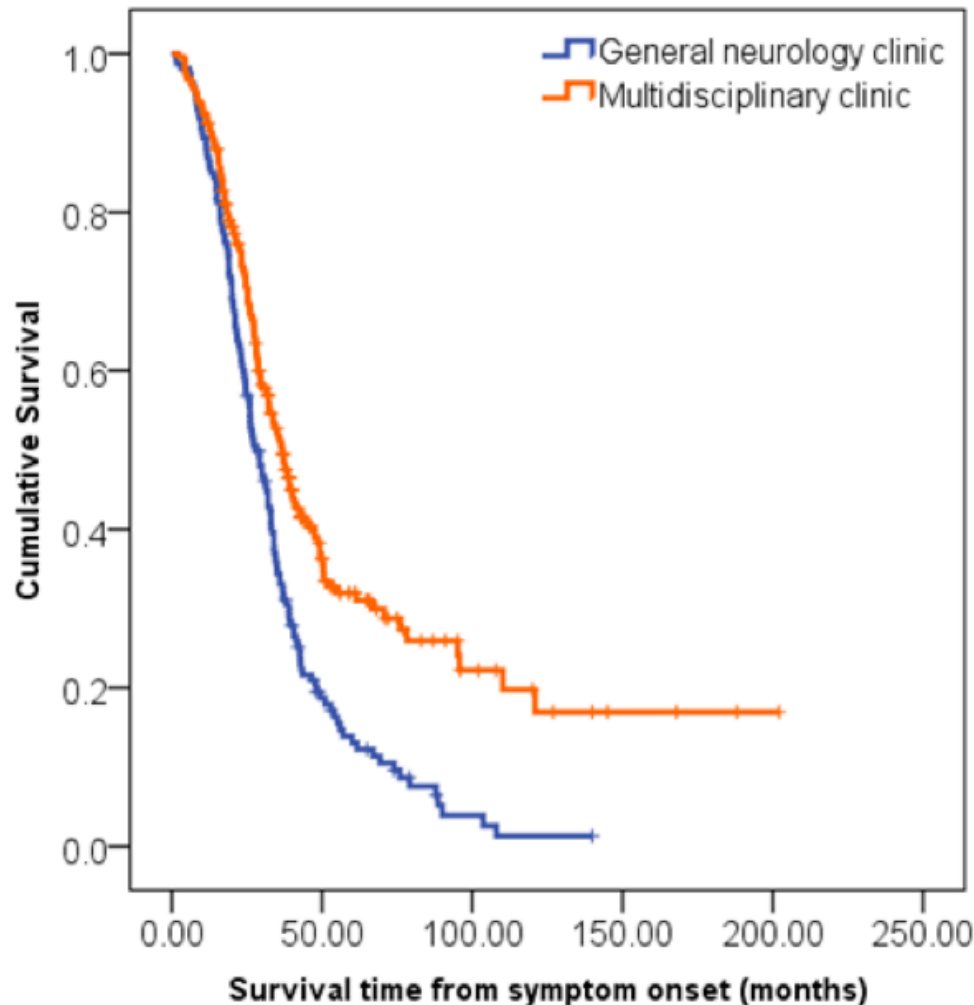
Motor Neuron Disease

- Commonest neurodegeneration of midlife
- Lifetime risk 1:400
- ~ 5% of cases in North of England have a family history
- 70% die within 1000 days of first symptom
- Most people have symptoms for 12 months before diagnosis

Outline

- Multidisciplinary (MDT) care
- Management of neuromuscular respiratory failure
- Nutrition
- Specific devices to support weakened muscles
- Prospects for improved neuroprotection in ALS/MND

Symptomatic care from a multidisciplinary team (MDT) improves survival



Survival of all MND patients from symptom onset who attended a general neurology clinic or the multidisciplinary clinic (months).

**Independent of PEG,
NIV, Riluzole**

- Aridegbe, McDermott, Shaw 2012 Sheffield, UK
- Van den Berg 2005 Utrecht, The Netherlands
- Chio 2006 Turin, Italy
- Traynor, Hardiman 2003 Dublin, Ireland

Outline

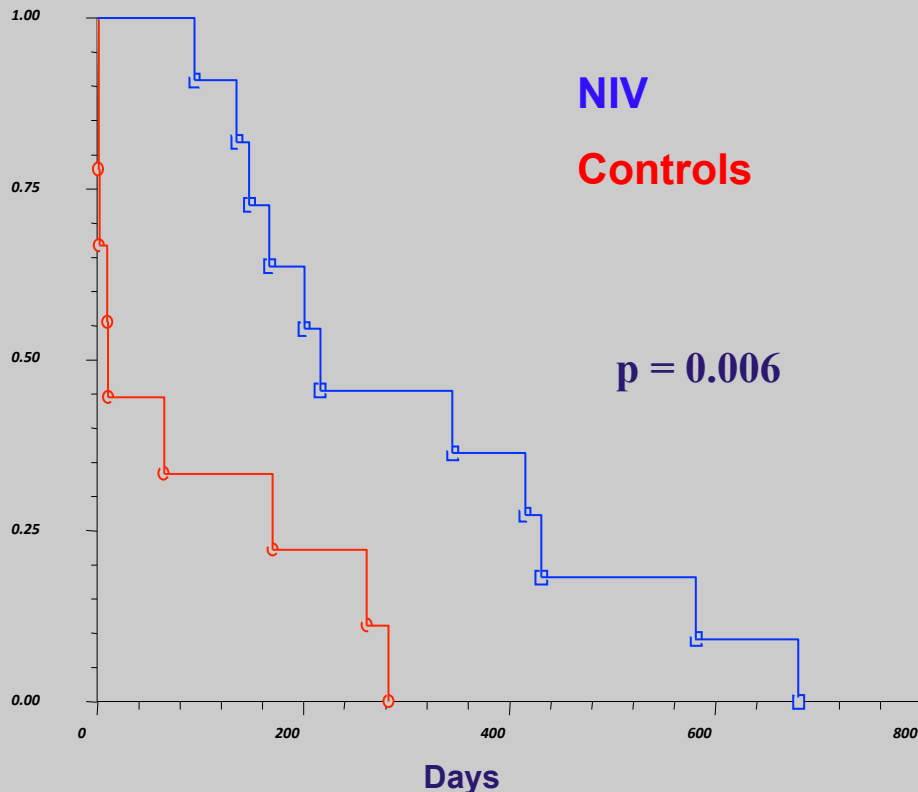
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Weakness of the Respiratory Muscles in MND

- Like any other skeletal muscle, respiratory muscles are also affected in motor neuron disease (MND)
- The major consequences of respiratory muscle weakness include:
 - Respiratory failure
 - Inability to cough effectively
- Respiratory insufficiency is the major cause of morbidity and mortality in MND
- Supporting respiratory function and preventing chest infections may prolong survival and improve quality of life

Randomised trial of non-invasive ventilation in MND

Improvement in life expectancy post randomisation



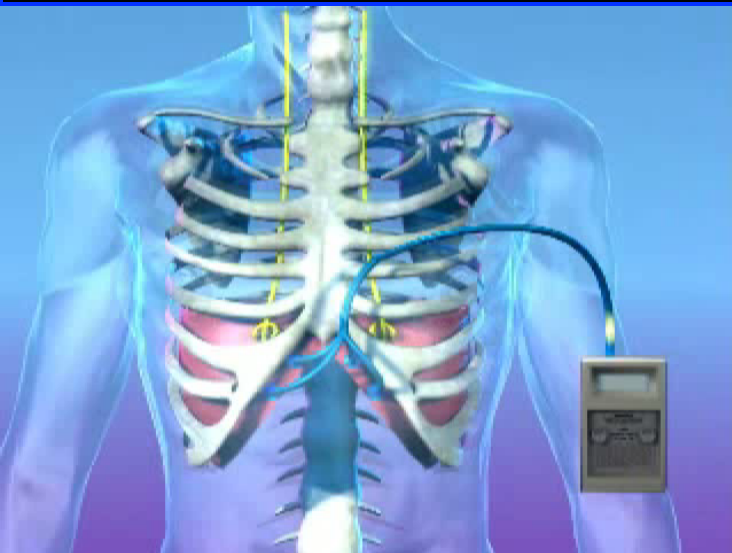
NICE GUIDELINE 2010

SC Bourke → T Williams, PJ Shaw* GJ Gibson* Lancet Neurology 2006

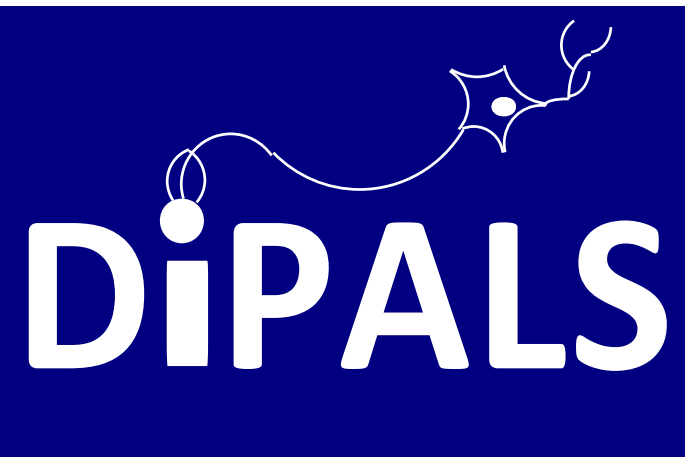
NIV is not problem free

- Compliance not 100%
 - Multifactorial
- Intrusive
- Cumbersome

Therefore an alternative would be attractive

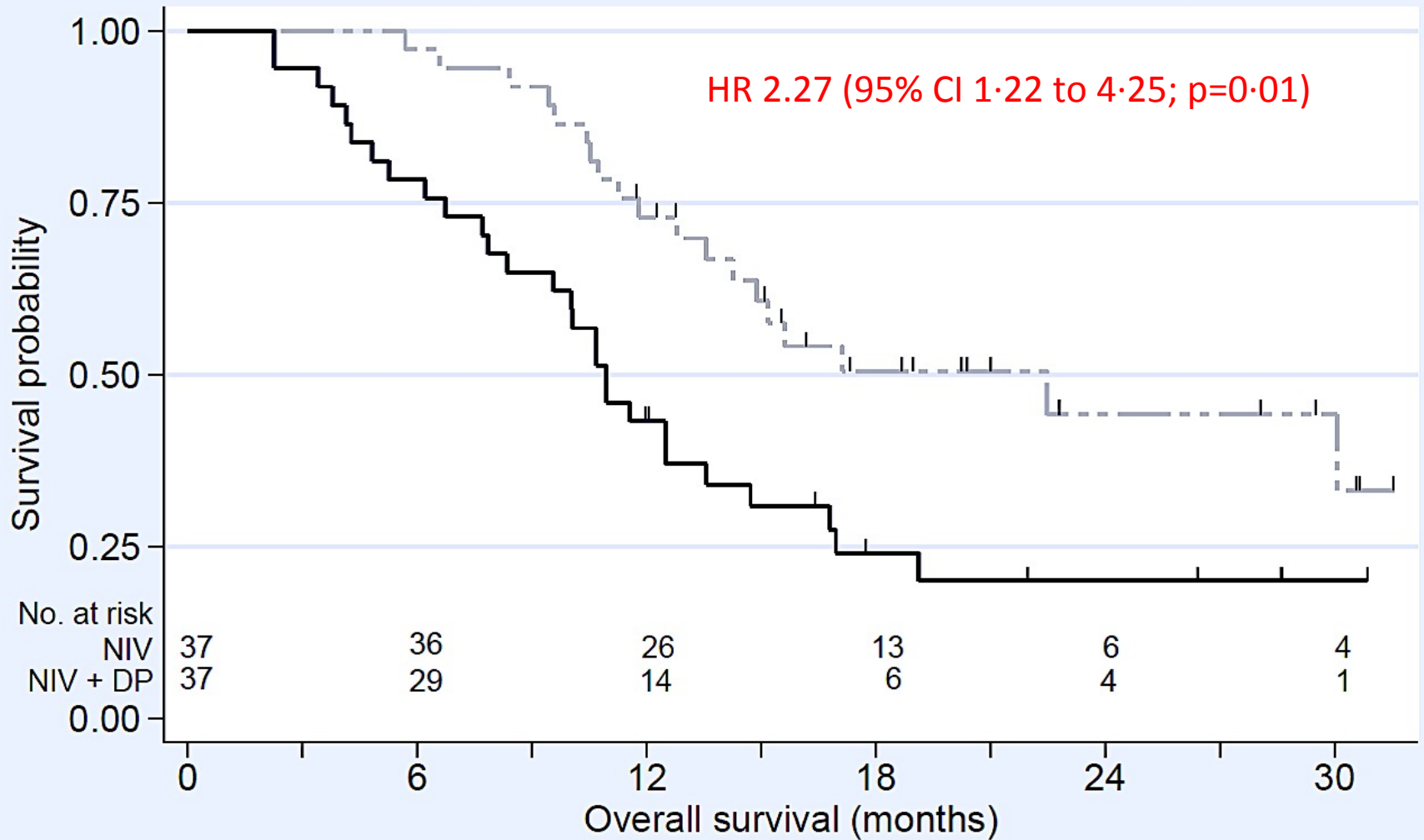


*A randomised controlled trial evaluating NeuRx/4
Diaphragm Pacing in patients with respiratory muscle
weakness due to Motor Neuron Disease or Amyotrophic
Lateral Sclerosis*



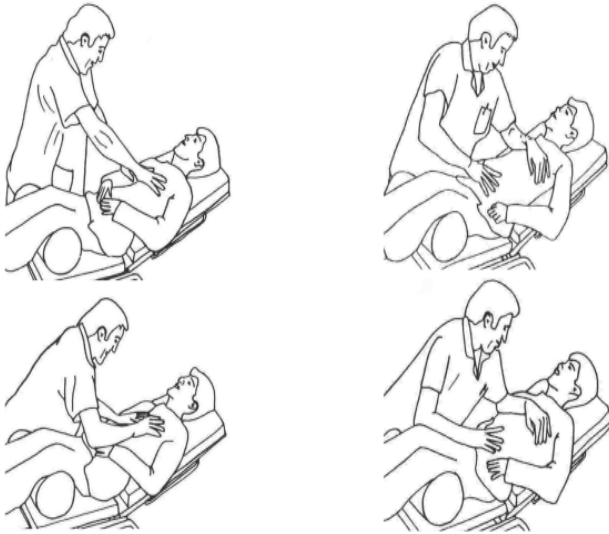
CI Dr Chris McDermott¹¹

Overall survival



Treatment arm - - - - - NIV ——— NIV+Pacing

Manually assisted cough via chest compressions and abdominal-thoracic compressions



Non-invasive aids for the management of weak respiratory muscles



BiPAP Ventilator



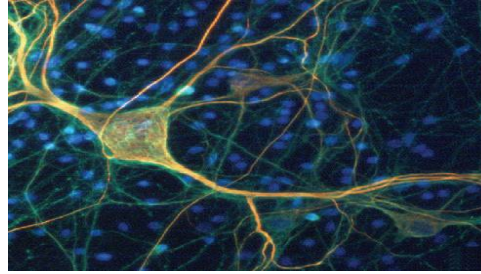
Mechanical in-exsufflator
Cost £4000



Manual insufflator
Cost £16



The
University
Of
Sheffield.



Effects of cough augmentation on morbidity,
quality of life and survival in patients with
motor neuron disease using non-invasive
ventilation:

A randomized clinical trial

ISRCTN 43911973

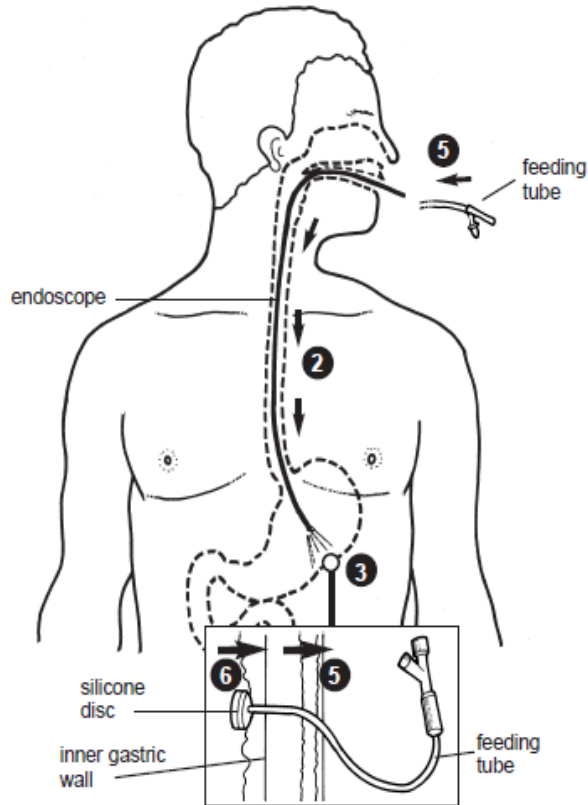
Future work

- A larger multi-centre study is required to explore the potential benefits of intervention with cough assist devices in order to make firm recommendations.
- The data generated and the lessons learned in this study will be valuable for power calculation and informing the inclusion criteria in the planning of a larger study
 - More stringent inclusion criteria based on effective use of NIV over ~ 4 weeks
 - Inclusion of peak cough flow in the minimisation criteria
- A larger study based on survival and QOL may be achievable with ~ 100 patients if M-IE assumed to convey a moderate/large effect size

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Percutaneous Endoscopic Gastrostomy (PEG)

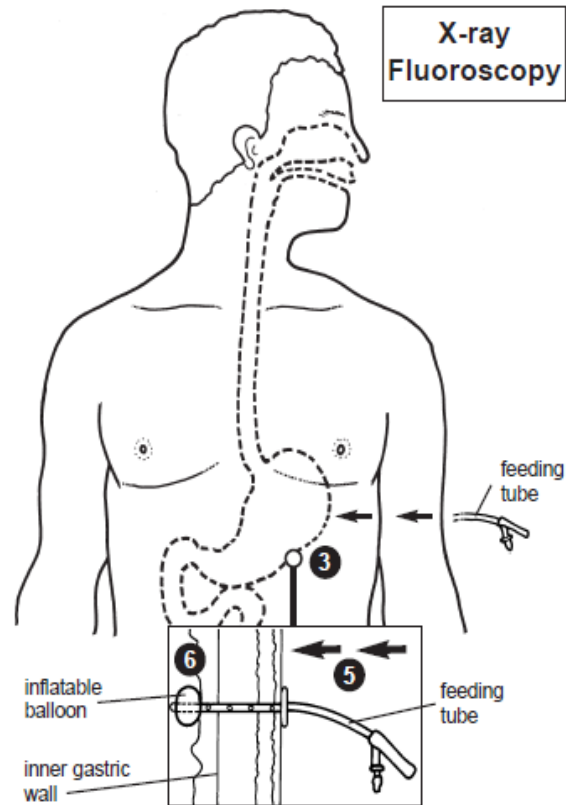


1. Conscious sedation (not shown in picture)
2. Endoscope insertion and stomach inflation
3. Transillumination with endoscope to locate puncture site
4. Incision, guide wire insertion (not shown in picture) through puncture site into stomach, up the oesophagus, exiting mouth
5. Feeding tube passed over the guide wire through the mouth, oesophagus, into stomach and pulled through the abdominal wall incision
6. Secure fixation with robust silicone disc
7. Endoscopic check

Advantages: Large bore tube placement, secure fixation, stitches not needed

Disadvantages: Endoscope use, conscious sedation, NIV use not possible during the procedure

Radiologically Inserted Gastrostomy (RIG)

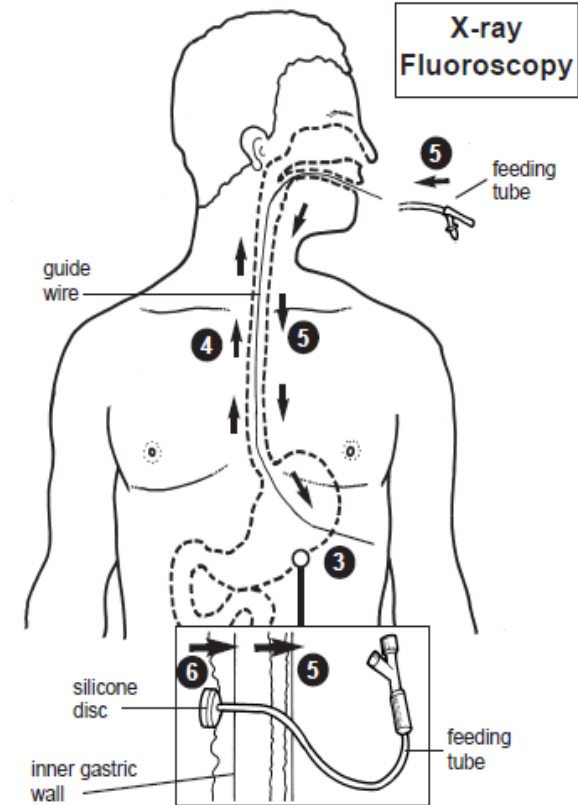


1. Conscious sedation not necessary (not shown in picture)
2. Stomach inflation with NGT (not shown in picture)
3. Location of puncture site under fluoroscopic guidance
4. Stomach stitched to the abdominal wall (gastropexy), guide wire pushed into stomach from outside, track enlargement through a series of dilators (not shown in picture)
5. Feeding tube pushed into stomach from outside through enlarged track
6. Feeding tube fixation with inflatable balloon
7. Fluoroscopic check with contrast medium injection

Advantages: No endoscope use, NIV use possible, conscious sedation not required

Disadvantages: Small bore tube placement, stitches needed

Per-oral Image-guided Gastrostomy (PIG)



1. Minimal conscious sedation (not shown in picture)
2. Stomach inflation with NGT (not shown in picture)
3. Location of puncture site under fluoroscopic guidance
4. Guide wire insertion through puncture site into the stomach, up the oesophagus, exiting mouth
5. Feeding tube passed over the guide wire through the mouth, oesophagus, into stomach and pulled through the abdominal wall incision
6. Secure fixation with robust silicone disc
7. Fluoroscopic check with contrast medium injection

Advantages: Minimal sedation, no endoscope use, NIV use possible, large bore tubes, secure fixation, stitches not needed

Disadvantages: More complex procedure

Gastrostomy benefits (?)

- Alternative nutritional intake route

Unanswered Questions

- Improved survival (?)
- Improved nutritional outcome (?)
- Improved quality of life (?)
- Most appropriate method (?)
- Optimal timing (?)

A prospective multi-centre evaluation of gastrostomy in patients with MND



PROGAS



Prof. Pam Shaw



Dr Chris McDermott



Dr Haris Stavroulakis

Conclusions

- Peri-procedural safety similar for PEG, RIG and PIG
- No significant differences in 30-day mortality rates
- 30-day mortality independent of insertion method but significantly higher for patients with more than 10% weight loss
- Differences in post-gastrostomy survival driven by MND progression
- Survival independent of gastrostomy method but significantly influenced by FVC, BMI and weight loss %
- PEG associated with higher peri-procedural complications but easier tube management
- RIG associated with higher post-procedural complications and more complex tube management
- PIG appears to be safe for frail patients with respiratory compromise

Recommendations

- Early gastrostomy placement before respiratory and clinical deterioration
- Timing and method selection based on individual needs
- Gastrostomy survival prediction tool is being generated based on FVC, BMI and % weight loss
- % Weight loss may provide the best guide for the timing of gastrostomy placement

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Tackling Neck Muscle weakness

- Head weighs ~ 5kg
- Existing support devices either immobilise the neck or provide insufficient support





headup



CI Dr Chris McDermott

END PRODUCT SSS COLLAR



S Baxter —————> *PJ Shaw, CJ McDermott J Rehab Res & Dev 2015*

*H Reed*²⁵ —————> *PJ Shaw, CJ McDermott J Med Engin & Technol 2015*

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THE SEARCH FOR NEUROPROTECTION

Recent Therapeutic Trials in MND

Anti-glutamate agents

- Riluzole *+
- Gabapentin +/-
- Lamotrigine
- Topiramate
- Ceftriaxone

Anti-oxidant therapy

- N-acetyl cysteine +/-
- Co-enzyme Q10

Anti-inflammatory/Inhibitors of astrocyte activation

- ONO 2506
- Celecoxib
- Copaxone

Neurotrophic factors

- CNTF
- IGF-1 +/-
- BDNF (SC and IT)
- GDNF

Antiapoptotic

- Talampanel
- Minocycline

Other

- Xaliproden/ SR 57746A
- Creatine
- Pentoxifylline
- Indinavir
- Lithium
- Olesoxime
- Dexpramipexole

TRIALS IN THE PIPELINE FOR ALS/MND

1. Two trials of muscle troponin activators:

Cytokinetics - tirasemtiv

Orion - levosimendan

2. Anti-oxidant edaravone -Phase 2/3 - Treeway.

3. SOD1 knock-down - anti-sense oligonucleotide Phase 1 Biogen.

Similar approach for C9ORF72 patients in development.

4. MIROCALS Phase 2 trial of low dose interleukin 2 as an anti-inflammatory agent.

5. Biogen Methodology Evaluation study - to assess the best outcome measures to use in Phase 2 trials.

Conclusions

- 1. Good symptomatic care improves survival and quality of life for patients with MND.
- 2. MDT care has an additional benefit above riluzole, NIV, PEG.
- 3. New aspects of respiratory management are being explored to provide an evidence base including: diaphragm pacing; cough assist devices; end of life care in patients with NIV.
- 4. Evidence based guidelines for optimal nutritional care / gastrostomy placement will emerge in the near future.
- 5. Bioengineering collaboration and assistive technology may generate devices to provide improved support for aspects of neuromuscular weakness eg better designed collars for neck support.

Key References

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